REMARKS

Claims 1-7, 9-32, 35-40, and 56-58 are pending in the above-identified patent application. Claims 8, 33-34, and 41-55 have previously been cancelled. Claims 1, 30, and 58 are amended in this response.

Claims 1-7, 9-32, 35-40, and 56-58 are subject to a Restriction Requirement and a Requirement for Election of Species.

The shortened statutory period for response to the Restriction Requirement and the Requirement for Election of Species has been extended to February 5, 2008 by the filing of a one-month Request for Extension of Time Under 37 C.F.R. § 1.136(a). Accordingly, this response is being filed in a timely manner.

I. AMENDMENTS TO THE APPLICATION

Entry of the amendments of the claims is respectfully requested. As detailed below, these amendments introduce no new matter.

Claim 1 is amended to state that the cells are stable in culture and do not undergo dedifferentiation in culture. Support for this limitation is found, e.g., at page 19, line 21 to page 20, line 4, of the original PCT application, stating that these cells can be passaged through 150 population doublings and retain their function in the proprietary media referred to. The retention of function implies lack of dedifferentiation, as the functions of these cells are the functions of differentiated hepatocytes. Support for this limitation is also found at page 42, lines 21-22 of the original PCT application, stating: "differentiated properties of immortalized hepatocytes are highly stable."

Claims 30 and 58 are amended to correct a minor error in subparagraph (9) of each claim. The "other livertropic virus" should properly be CMV, not "HCV". CMV was recited in the originally filed claims, but through a typographical error, HCV was recited here. The source of this error is clear, as HCV is already recited in these claims under the category of hepatitis viruses.

Accordingly, entry of these amendments is respectfully requested.

II. THE RESTRICTION REQUIREMENT

Restriction was required under 35 U.S.C. §§ 121 and 372.

The Restriction Requirement stated that this application contained the following inventions or groups of inventions that were not so linked as to form a single inventive concept under PCT Rule 13.1.

In accordance with 37 C.F.R. § 1.499, Applicants were required to elect a single invention to which the claims must be restricted.

Group I is claims 1-7 and 9-32, drawn to a virally-immortalized hepatocyte.

Group II is claims 35-40 and 56-57, drawn to a first method of using a virally-immortalized hepatocyte to assess the effects of a chemical entity on the liver.

Group III is claim 58, drawn to 22 various assay procedures wherein each procedure relies upon the use of a virally-immortalized hepatocyte.

The Restriction Requirement stated that the inventions listed as Groups I through III do not relate to a single inventive concept under PCT Rule 13.1 because,

under PCT Rule 13.2, they lack the same or corresponding technical features for the following reasons:

The special technical feature of a virally-immortalized hepatocyte, according to the Restriction Requirement, was known in the prior art. For example, according to the Restriction Requirement, U.S. Patent No. 6,107,043 to Jauregui et al. ("Jauregui et al. '043") and U.S. Patent No. 6,046,050 to Strauss et al. '050 ("Strauss et al. '050") both disclosed virally-immortalized hepatocytes that are derived from normal liver cells, were non-tumorigenic, and had normal metabolic activity and/or produced plasma proteins. Therefore, according to the Restriction Requirement, the unifying or corresponding technical feature was known, leading to a lack of unity of the invention.

III. RESPONSE TO THE RESTRICTION REQUIREMENT

In response to the Restriction Requirement, Applicants respond as follows:

Applicants hereby elect the invention of Group I, claims 1-7 and 9-32, drawn to a virally-immortalized hepatocyte, for prosecution on the merits, with traverse.

The Restriction Requirement is traversed on the following grounds:

Firstly, neither of the references cited in the Restriction Requirement, namely Jauregui et al. '043 or Strauss et al. '050, disclose or suggest the special technical feature recited in claim 1, as amended herein. This special technical feature is a virally-immortalized hepatocyte that possesses all of these four properties: (1) being derived from a normal liver cell; (b) being nontumorigenic; (3) naturally producing endogenous therapeutic plasma proteins (TPPs); and (4) being stable in culture and not undergoing dedifferentiation in culture.

With respect to Jauregui et al. '043, none of the five cell lines disclosed therein, namely Lines I through V, was shown to naturally produce any endogenous therapeutic plasma proteins. There was no assay conducted for either expressed proteins or mRNA encoding such proteins. Although such cells did show some P450 metabolic activity, the presence of P450 metabolic activity, in and of itself, cannot be taken to lead to the conclusion that the cells produce any endogenous therapeutic plasma proteins.

Moreover, with respect to Jauregui et al. '043, none of these cell lines was shown to be stable in culture and not undergo dedifferentiation in culture. One result in Jauregui et al. '043 is particularly significant. At least for Line I, subclone D63H was partially aneuploid, with 30-38 chromosomes after passage 31 (Jauregui et al., column 5, lines 2-3), as compared with 38 for normally diploid porcine somatic cells. The loss of chromosomes is common in cultured cells and is frequently associated with instability and dedifferentiation in culture. There is no teaching or suggestion in Jauregui et al. '043 that providing inducible expression of SV40 TAg (Line II), using a temperature-sensitive Tag gene (Line III), or including DNA encoding the tumor suppressor p53 (Lines IV and V) would overcome this problem. Specifically, for Line III, proliferation ceases when the Tag activity is blocked by the use of the non-permissive temperature, again raising a question about the long-term stability of such a cell line.

Therefore, the special technical feature described above is not taught or suggested by Jauregui et al. '043.

Similarly, the special technical feature described above is not taught or suggested by Strauss et al. '050. Firstly, although Strauss et al. '050 was weakly positive for α_1-antitrypsin (Strauss et al. '050, Table 1), there was no showing that the cells were actually producing α_1-antitrypsin after culture and subcloning. This weak positive result may well have come from prior production of α_1-antitrypsin which was retained in the cytoplasm of the cells, even though the cells were no longer producing this protein.

Secondly, there was absolutely no showing in Strauss et al. '050 that the cells described therein were nontumorigenic. As the action of p53 is well known to be a tumor suppressor, and the expression of p53 was blocked by the use of an antisense mechanism, there is an extremely high risk that these cells were in fact potentially tumorigenic. In fact, there was no showing whatsoever that the cells of Strauss '050 were in fact nontumorigenic.

Thirdly, there was no showing in Strauss et al. '050 that the cells described therein were stable in culture and failed to undergo dedifferentiation. The fact that these cells required the blocking of the expression of the tumor suppressor p53 to prevent apoptosis and cell death raised the question of their long-term stability in culture. Strauss et al. '050 failed to show that the cells described therein were stable in culture, or that they avoided dedifferentiation.

Therefore, Applicants assert that all pending claims do possess a special technical feature in common that is not disclosed or suggested by the prior art. Accordingly, the Examiner is respectfully requested to withdraw the Restriction Requirement.

In addition, the Restriction Requirement is traversed on the following grounds:

Firstly, the Examiner has not met the burden for demonstrating the necessity for restriction. M.P.E.P. § 803 requires for restriction both: (1) that the inventions are independent or distinct as claimed; and (2) that there would exist a "serious burden" on the Examiner if all of the claims were examined in one application. These requirements have not been met.

In fact, the subject matter of Groups I through III, claims 1-7, 9-32, 35-40, and 56-58, are sufficiently related to avoid restriction, because there would be no "serious

burden" on the Examiner if all of the claims were examined together in one application. The essence of the invention is the immortalized hepatocytes of claim 1, and other claims merely define these hepatocytes and describe the metabolic activities carried out by these hepatocytes, as well as the use of these hepatocytes to carry out assays related to their activities.

Accordingly, the subject matter of the invention is sufficiently interrelated that no serious burden on the Examiner would exist if all the claims were examined on the merits. That is because the relevant art involved, if any relevant art exists, largely overlaps for these claims. For example, any publications, patents, or published patent applications describing hepatocytes whose properties would be relevant for the novelty or nonobviousness of the subject matter of the claims of Group I would be likely to discuss the metabolic activities of such hepatocytes and the suitability of such hepatocytes for assays that could be carried out by the use of cultured hepatocytes. This statement is not to be taken as an admission that any such prior art exists, merely a statement that, should any relevant art exists, it is likely to be relevant to the subject matter of more than one group of claims.

Therefore, there is no basis for restriction of the claims based on the existence of a "serious burden" to the Examiner that would exist if the subject matter of all claims were examined on the merits.

Applicants do not traverse the Restriction Requirement on the grounds of lack of patentable distinctness. Rather, Applicants traverse the Restriction Requirement on the grounds that the inventions of Groups I through III are sufficiently related that restriction is not properly required, despite the possible existence of patentable distinctness.

Therefore, the Restriction Requirement is respectfully traversed and the Examiner is respectfully requested to withdraw the Restriction Requirement and to allow the examination of all of Groups I through III on the merits.

IV. THE REQUIREMENT FOR ELECTION OF SPECIES

This application was stated, in the Requirement for Election of Species, to contain more than one species of the generic invention. These species were deemed, in the Requirement for Election of Species, to lack unity of invention because they were not so linked as to form a single general inventive concept under PCT Rule 13.1. The species were assays (1) through (22) of claim 58. This claim was stated to be generic. The Requirement for Election of Species stated that in order for more than one species to be examined on the merits, additional examination fees would have to be paid.

V. RESPONSE TO THE REQUIREMENT FOR ELECTION OF SPECIES

In response to the Requirement for Election of Species, Applicants respond as follows:

Because Group I, claims 1-7 and 9-32, drawn to a virally-immortalized hepatocyte, was elected for prosecution on the merits, with traverse, the Requirement for Election of Species is moot unless the Examiner withdraws the Restriction Requirement. This is because the Requirement for Election of Species applies only to claim 58 within Group III.

In the event that the Examiner, as requested, withdraws the Restriction Requirement and allows consideration of Group III (claim 58) on the merits, Applicants

hereby elect assay (20), studies of cytotoxicity of drugs, chemical entities, carcinogens, and xenobiotics, for prosecution on the merits, with traverse.

No additional examination fees are paid.

The Requirement for Election of Species is traversed on substantially the same grounds as the Restriction Requirement. That is, the references relied upon do not teach or suggest the special technical feature of claim 58.

Claim 58 is a dependent claim dependent from claim 1 and thus incorporates all the limitations of claim 1. Therefore, the discussion above about the failure of Jauregui et al. '043 and Strauss et al. '050 to teach or suggest the special technical feature of claim 1 is also applicable to claim 58. Therefore, these species possess unity of invention because they are so linked as to form a single general inventive concept under PCT Rule 13.1. The linkage comes about through the use of the cells of claim 1 in the assays of claim 58. Therefore, the special technical feature of claim 1 is also present in claim 58, and this special technical feature is not taught or suggested by Jauregui et al. '043 and Strauss et al. '050.

Additionally, because assays (1) through (22) of claim 58 all recite the use of the virally immortalized hepatocytes of claim 1, these species are sufficiently related to negate a requirement for the election of species. That is because, as described above, a "serious burden" would not exist on the Examiner if all of these species were examined in a single application. As detailed above, the relevant prior art, if any such relevant prior art in fact exists, would largely overlap for the examination of assays (1) through (22) on the merits for claim 58.

As with the Restriction Requirement, Applicants do not traverse the Requirement for Election of Species on the grounds of lack of patentable distinctness. Rather, Applicants traverse the Requirement for Election of Species on the grounds that

the inventions of assays (1) through (22) of claim 58 are sufficiently related that restriction is not properly required, despite the possible existence of patentable distinctness.

Additionally, it is submitted that claim 58, which is generic, is allowable. Claim 58 is dependent on claim 1 and incorporates all the limitations of that claim, and is thus allowable.

In summary, should the Restriction Requirement be withdrawn and claim 58 examined on the merits, assay (20) is elected for prosecution on the merits. However, should claim 58 (Group III of the Restriction Requirement) be examined on the merits, the Requirement for Election of Species is also traversed on substantially the same grounds as the Restriction Requirement.

VI. CONCLUSION

In conclusion, the subject matter of Group I, claims 1-7 and 9-32, drawn to a virally-immortalized hepatocyte, is elected for prosecution on the merits, with traverse.

The Examiner is respectfully requested to withdraw the Restriction Requirement and examine all of Groups I-III on the merits.

With respect to the Requirement for Election of Species, in the event that the Restriction Requirement is withdrawn and claim 58 is examined on the merits, assay (20) is elected for prosecution on the merits, with traverse.

In the event that the Restriction Requirement is withdrawn and claim 58 is examined on the merits, the Examiner is also respectfully requested to withdraw the

Requirement for Election of Species and examine all of assays (1)-(22) recited in claim 58 on the merits.

If any issues remain, the Examiner is respectfully requested to telephone the undersigned at (858) 450-0099 x302.

Respectfully submitted,

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